

102. (NEW) The protein of Claim 18, wherein the modification further comprises a mutation at Phe309.

103. (NEW) The protein of Claim 18, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

104. (NEW) The protein of Claim 18, wherein the amino acid sequence spacer is 54 residues in length.

105. (NEW) The protein of Claim 104, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

BA 106. (NEW) The protein of Claim 105, wherein the residue at position 794 is threonine.

1-7 Sub D 107. (NEW) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification consists of a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3- domains.

18 108. (NEW) The protein of Claim 107, wherein the modification further consists of a substitution of the Arg residue at position 336 with Ile and a substitution of the Arg residue at position 562 with Lys.

109. (NEW) The protein of Claim 107, wherein the modification further consists of a mutation at Phe309.

110. (NEW) The protein of Claim 107, wherein the mutation consists of a substitution of Arg at position 740 with Ala.

Sub 4 111. (NEW) The protein of Claim 107, wherein the amino acid sequence spacer is 54 residues in length.

112. (NEW) The protein of Claim 111, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

B 113. (NEW) The protein of Claim 112, wherein the residue at position 794 is threonine.

114. (NEW) The protein of Claim 108, wherein the modification further consists of a mutation at Phe309.

115. (NEW) The protein of Claim 108, wherein the mutation consists of a substitution of Arg at position 740 with Ala.

116. (NEW) The protein of Claim 108, wherein the amino acid sequence spacer is 54 residues in length.

117. (NEW) The protein of Claim 116, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

118. (NEW) The protein of Claim 117, wherein the residue at position 794 is threonine.

119. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 18 in admixture with a parenterally acceptable vehicle or excipient.

120. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 107 in admixture with a parenterally acceptable vehicle or excipient.

121. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 108 in admixture with a parenterally acceptable vehicle or excipient.

122. (NEW) A method for treating hemophilia comprising the steps of administering a procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3- domains.

123. (NEW) The method of Claim 122, wherein the modification of the protein further comprises a substitution of the Arg residue at position 336 with Ile and a substitution of the Arg residue at position 562 with Lys.

124. (NEW) The method of Claim 122, wherein the modification further comprises a mutation at Phe309.

125. (NEW) The method of Claim 122, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

126. (NEW) The method of Claim 122, wherein the amino acid sequence spacer is 54 residues in length.

127. (NEW) The method of Claim 126, wherein the amino acid sequence spacer comprises residues 791 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

128. (NEW) The method of Claim 127, wherein the residue at position 794 is threonine.

129. (NEW) The method of Claim 123, wherein the modification further comprises a mutation at Phe309.

130. (NEW) The method of Claim 123, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

131. (NEW) The method of Claim 123, wherein the amino acid sequence spacer is 54 residues in length.

132. (NEW) The method of Claim 131, wherein the amino acid sequence spacer comprises residues 791 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

133. (NEW) The method of Claim 132, wherein the residue at position 794 is threonine.

BS 134. (NEW) A method for treating hemophilia comprising the step of administering a procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification consists of a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3- domains.

135. (NEW) The method of Claim 134, wherein the modification further consists of a substitution of the Arg residue at position 336 with Ile and a substitution of the Arg residue at position 562 with Lys.

136. (NEW) The method of Claim 134, wherein the modification further consists of a mutation at Phe309.

137. (NEW) The method of Claim 134, wherein the mutation consists of a substitution of Arg at position 740 with Ala.

138. (NEW) The method of Claim 134, wherein the amino acid sequence spacer is 54 residues in length.

139. (NEW) The method of Claim 138, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

B¹
140. (NEW) The method of Claim 139, wherein the residue at position 794 is threonine.

141. (NEW) The method of Claim 135, wherein the modification further consists of a mutation at Phe309.

142. (NEW) The method of Claim 135, wherein the mutation consists of a substitution of Arg at position 740 with Ala.

143. (NEW) The method of Claim 135, wherein the amino acid sequence spacer is 54 residues in length.